lines 4-13. Support for the recitation "dry powder particles" in amended Claim 20 is found, for example, at page 5, lines 22-29 and page 13, lines 1-24.

Support for new Claims 45-51 is found throughout the specification.

Support for the recitation "at least 50% of the particles have a fine particle fraction less than 4.0 μm" in new Claims 45 and 47 is found, for example, at page 27, lines 5-19, at page 33, line 7 to page 34, line 7, and Figure 3.

Support for the recitation "at least 75% of the particles have a fine particle fraction less than 6.8 μm" in new Claims 46 and 48 is found, for example, at page 28, line 18 to page 29, line 4, page 37, line 22 to page 38, line 9, and Figure 6.

Support for new Claims 49 and 50 is found, for example, at page 30, lines 10-21.

Support for new Claim 51 is found, for example, at page 5, lines 11-13.

Thus, the amendments to Claims 1 and 20 and new Claims 45-51 are supported by the application as filed. Therefore, this Amendment adds no new matter.

Additional remarks addressing the Examiner's rejections are set forth below.

Rejection of Claims 1-19 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the Examiner's opinion, "Claim 1 is vague and indefinite because it is not clear what '50% of the mass' means." Office Action, page 2, lines 9-10.

The second paragraph of 35 U.S.C. § 112 requires only that the claims "set out and circumscribe a particular area with a reasonable degree of precision and particularity." In re Moore and Janoski, 169 USPQ 236, 238 (CCPA 1971). The Examiner is reminded that the meaning of the claims is not analyzed in a vacuum, but in light of the teachings of the prior art and of the specification as it would be interpreted by one possessing the ordinary level of skill in the pertinent art. Id. at 238.

Applicants' specification clearly conveys what is meant by the recitation "deliver at least about 50% of the mass of particles". For example, Applicant's specification teaches:

> As used herein, the term "emptied" means that at least 50% of the particle mass enclosed in the receptacle is emitted from the inhaler during administration of the particles to a subject's respiratory system.

Specification, page 12, lines 25-27.

Applicants' specification further teaches:

> In one embodiment of the invention, at least 50% of the mass of the particles stored in the receptacle are delivered to a subject's respiratory tract in a single, breath-activated step.

Specification, page 16, lines 5-7.

Nevertheless, in order to expedite prosecution, Claim 1 has been amended to recite "at least about 50% of the mass of particles stored in the receptacle is delivered to the pulmonary system of the subject." In view of the clear teachings in Applicants' specification and the standard for analyzing claimed subject matter as set out in Moore and Janoski, it is clear that the person of ordinary skill in the art would understand Applicant's claimed method. Therefore, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-44 Under 35 U.S.C. § 103(a)

Claims 1-44 are rejected under 35 U.S.C. § 103(a) as being obvious in view of Maa *et al.* (U.S. Patent No. 6,284,282 B1). The Examiner states that Maa *et al.* teach "methods of preparing a dry powder composition comprising spray freeze-drying an aqueous mixture of a protein" and "administering a therapeutically effective dose of a therapeutic protein to a patient comprising administering to the alveolar regions of the lungs of a patient a spray freeze dried therapeutic protein dry powder composition." Office Action, page 3, lines 11-16. The Examiner further states that "[t]he term 'powder' is described as a composition that consists of finely dispersed solid particles" and that "[t]he average particle size ranges from about 5 μm to about 30 μm [and] the preferred average particle size is 6-8 μm". Office Action, page 3, lines 17-22. The Examiner states that the FPF (which is the fine particle fraction, and not the fine powder

fraction as stated by the Examiner (see Maa *et al.*, column 5, lines 57-59) and is defined by Maa *et al.* as powder with an aerodynamic mass median diameter less than 6.8 μm as determined using a multiple-step liquid impinger with a glass throat through a dry powder inhaler (see Maa *et al.*, column 5, lines 59-65)), is preferably at least 10%, and especially preferred at 40 to 50%, and that the particles have a tap density of less than about 0.8 g/cm^3, with tap densities of less than 0.4 g/cm^3 being preferred, and less than about 0.1 g/cm^3 being especially preferred. Office Action, page 3, line 22 to page 4, line 4.

According to the Examiner, although Maa *et al.* do not specifically disclose the mass of the particles delivered, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the teachings of Maa *et al.* "by concentrating on more specific volumes of receptacle and mass of particles delivered because knowing the specific values regarding dosages in treating certain disorders is very important and helpful to the health care providers and patients." Office Action, page 4, lines 14-20.

A finding that the claimed invention is obvious under 35 U.S.C. § 103 requires that (1) "the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process;" and (2) that "the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." Id. (emphasis added). Further, when determining patentability under 35 U.S.C. § 103, the prior art must be considered as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). To establish *prima facie* obviousness, the prior art must also teach or suggest all of the claim limitations. In re Royka, 180 USPQ 580 (CCPA 1974).

As explained below, Applicants' claimed method of delivering a therapeutic dose of a bioactive agent to the pulmonary system in a single breath-activated step is not *prima facie* obvious because the cited reference: (i) fails to teach or suggest all of the claim limitations; and (ii) fails to provide the requisite reasonable expectation of success.

i) Failure to Teach All of the Claim Limitations

As stated by the Examiner, Maa *et al.* do not specifically disclose the mass of the particles that are delivered to the pulmonary system. Office Action, page 4, lines 14-16. However, in the Examiner's opinion, it would have been obvious to the person of ordinary skill in the art to modify the teachings of Maa *et al.* to concentrate on the mass of particles delivered to the pulmonary system because dosage is an important element in treating certain disorders. Office Action, page 4, lines 16-20.

The Examiner states that Maa *et al.* teach a powder which is respirable and suitable for pulmonary delivery, wherein the particles have an average size ranging from about 5-30 μm, with a preferred size of 6-8 μm, and wherein the fine particle fraction (less than 6.8 μm) is preferably at least 10% and especially 40 to 50%. Office Action, page 3, line 20 to page 4, line 1. While Maa *et al.* generically teach such criteria, the Examples section of their specification teaches that the dispersion measurements of their particulate powders were calculated using a 10:1 (lactose carrier:powder) blend. Specifically, in Example 1 Maa *et al.* teach:

> Preparation of Blends Before powder dispersion measurement, each powder was blended with a lactose carrier (200M, DMV) at the 10:1 (carrier:powder) weight ratio by mixing using a tumbling mixer (Turbula, Glen Mill) and sieving using a stainless steel sieve (250 μm). The blend was first mixed for 5 min and then sieved by tapping. Some clumps were gently pressed through the sieve to deagglomerate the particles. The same mixing and sieving procedures were repeated for the second time.
> Powder Dispersion by Liquid Impingement The dispersibility of each powder/carrier blend was assessed using the multiple-stage liquid impinger through a dry powder inhaler (Dryhaler, Dura Corp., San Diego, Calif.) as shown in FIG. 2. All four stages were loaded with 25 mL water before experiment. Ten doses (10-20 mg each) of the blend sample were weighed out and loaded individually directly into the dose chamber of the device. The powder was dispersed at an inspiration rate of 60 L/min. The amount of protein deposited on the throat, four stages of the impinger, and the filter, as well as the amount retained in the device was assayed by measuring the UV absorbance at 280 nm using an absorptivity of 1.6 $cm^{-1}(mg/mL)^{-1}$. The percentage of the

> total dose collected on the third and the fourth stages and on the filter, representing the particles with the aerodynamic diameter ≤ 7 μm, was considered as the fine particle fraction.
> Powder Dispersion by Cascade Impaction The Anderson cascade impactor (FIG. 3a, 8 stage 1 ACFM Non Variable Particle Size Sampler Mark II) was also used to determine the dispersibility of each powder/carrier blend through a dry powder inhaler (Dryhaler, Dura Corp.).

Maa *et al.*, column 17, lines 38-67; emphasis added.

Similarly, in Example 2, which teaches the spray freeze drying of IGF-I, Maa *et al.* state:

> The spray freeze-dried powder was blended with 100M lactose coarse carrier at 1:10 weight ratio of active rhIGF-I to coarse carrier by mixing (Turbula, Glenn Mill) and sieving (250-μm mesh). Ten individuals of pre-weighted samples of 10 mg blended powder (or 5 mg raw powder) were loaded into a dry powder inhaler (Dura Pharmaceuticals, San Diego) and dispersed into a multi-stage liquid impinger (MSLI) at an air flow rate of 60 L/min and an inhalation time of 5 seconds, as outlined above.

Maa *et al.*, column 26, lines 15-18; emphasis added.

Thus, Maa *et al.* teach that a 10:1 (lactose carrier:powder) blend resulted in the particulate powders exhibiting particular desired physical and aerodynamic properties (e.g., median particle size, residual moisture, fine particle fraction). Maa *et al.*, column 18, lines 42-45, column 19, Table 1. Maa *et al.* further teach that their particulate powders exhibited the desired physical and aerodynamic properties due to the presence of the lactose carrier particles. Specifically, Maa *et al.* teach:

> The spray-freeze dried powder was blended with 100 M lactose carriers prior to fine particle fraction (<6.8 μm) measurement using a multi-stage liquid impinger model. Blending can theoretically improve the fine powder's flow properties. Small particles tend to interact with themselves (agglomeration) and with any contact surfaces due to high surface energy. Agglomerated particles behave like large particles and are difficult to be dispersed. Sticking to other contact surfaces results in material loss and poor powder flowability. If the interaction between the spray-dried particle (raw powder) and the carrier particle ($F_{r\text{-}c}$) overcomes the interaction among the raw powder (F_{rr}), it can result in homogeneous blending, thereby enhancing the powder's

> flowability. The next hurdle to jump is that these fine particles should be able to be deagglomerated from the carrier particle upon inhalation, i.e., the inhalation force can overcome F_{r-c}. Factors affecting these interactions are highly complicated.

Maa *et al.*, column 27, lines 6-25, emphasis added.

Thus, in contrast to independent Claim 1 and claims dependent thereon (Claims 2-19, 45, 46, and 49) of the subject application, Maa *et al.* clearly do not teach or suggest a method of delivering a therapeutic dose of a bioactive agent to the pulmonary system, in a single breath, wherein at least about 50% of the mass of particles stored in the receptacle is delivered to the pulmonary system of the subject. This is because the powders that Maa *et al.* analyzed were blends of a 10:1 weight ratio of lactose carrier:powder. Clearly, the large lactose particles comprising greater than 90% of the mass of the blend are not delivered to the pulmonary system of the subject and instead are used to improve the flow and dispersibility properties of the powder.

As described in the specification, Applicant's invention has the advantage that a large single dose of an agent (e.g., a therapeutic agent, a prophylactic agent, a diagnostic agent, a prognostic agent) can be delivered to the pulmonary system in a single breath with high efficiency (Specification, page 7, lines 11-29). In contrast, Maa *et al.* teach that the measured physical, aerodynamic and flow properties of their powder preparations (e.g., agglomeration, flowability, fine particle fraction) are due to the presence of large lactose carrier particles (which are present in a 10:1 weight ratio of lactose carrier:powder) in their blended preparations. Therefore, it is clear that Maa *et al.* do not teach or suggest all of the claim limitations of Claims 1-19, 45, 46 and 49 (e.g., wherein at least about 50% of the mass of particles stored in the receptacle is delivered to the pulmonary system of the subject).

ii) Failure to Provide Requisite Reasonable Expectation of Success

As described above, it is necessary to consider the prior art as a whole, including portions that would lead away from the claimed invention, when determining patentability under 35 U.S.C. § 103. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). With respect to Claims 1-19, 45, 46 and 49,

and in view of the teachings of Maa *et al.* that the desired physical, aerodynamic and flow properties of their powder are due to the presence of large lactose carrier particles, the person of ordinary skill in the art would not have had a reasonable expectation of success in delivering at least about 50% of the mass of particles stored in the receptacle to the pulmonary system of the subject, by modifying the teachings of Maa *et al.* to eliminate or greatly reduce the quantity of carrier particles (a necessary requirement to achieve delivery of at least 50% of the mass of the particles stored in the receptacle). This is because, as taught by Maa *et al.*, "[s]mall particles tend to interact with themselves (agglomeration) and with any contact surfaces due to high surface energy" and "[a]gglomerated particles behave like large particles and are difficult to be dispersed." Maa *et al.*, column 27, lines 9-13. Thus, the teachings of Maa *et al.*, taken as a whole, actually teach away from Applicants' claimed invention by teaching and exemplifying that the desired physical, aerodynamic and flow properties of their powder are due to the presence of the large lactose carrier particles (present in a 10:1 weight ratio; large lactose carrier:powder). Therefore, with respect to Claims 1-19, 45, 46 and 49 of the subject application, it is clear that Maa *et al.*, when considered in its entirety, fails to provide the requisite reasonable expectation of success which is necessary to establish a *prima facie* case of obviousness. In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Similarly, in contrast to independent Claim 20 and claims dependent thereon (Claims 21-44, 47, 48, 50 and 51) of the subject application, Maa *et al.* clearly do not teach or suggest a method of delivering a therapeutic dose of a bioactive agent to the pulmonary system, in a single breath, wherein at least about 5 milligrams of the bioactive agent is delivered to the pulmonary system of the subject. The Examiner is of the opinion that although Maa *et al.* do not specifically disclose the mass of the particles that are delivered to the pulmonary system, it would have been obvious to the person of ordinary skill in the art to modify the teachings of Maa *et al.* to concentrate on the mass of particles delivered to the pulmonary system because dosage is an important element in treating certain disorders. Office Action, page 4, lines 16-20.

As described in the specification, Applicant's invention has the advantage that a large single dose of an agent (e.g., a therapeutic agent, a prophylactic agent, a diagnostic agent, a prognostic agent) can be delivered to the pulmonary system in a single breath-activated step with

high efficiency (Specification, page 5, lines 4-8). Applicant's specification further describes the teachings of Cipolla *et al.* and states that "[c]urrently, the amount of drug that can be delivered to the lung in a single breath, via liquid or dry powder inhalers, generally does not exceed 5 mg (Cipolla, *et al.*, *Resp. Drug Delivery*, VII 2000:231-239 (2000); Reference AS, of record)." Specification, page 4, lines 18-20.

The teachings of Cipolla *et al.* elaborate on the difficulties associated with delivering high doses of drugs to the lungs.

> While metered dose and dry powder inhalers (MDIs and DPIs) have convenience advantages over nebulizers for the treatment of chronic disease, the requirement for high lung dose makes using such "bolus" systems challenging. The traditional MDIs and DPIs have generally been marketed for delivery of small doses of drugs to the airways to treat lung disease. ...A new generation of powders with better flow properties and improved dispersibility may lead to higher deposition efficiencies. However, in order to stabilize the protein or other therapeutic agent in the dry state, and to ensure good deagglomeration properties, additional excipients are frequently required. Often the active drug represents only a small fraction of the formulation; e.g., with the "AIR" technology for manufacturing porous dry particles, only 4% for albuterol sulfate, 10% for estradiol and 5% for insulin particles. So although the delivery efficiency is increased relative to that of the older generation dry powder formulations, the low drug loading may still present challenges to deliver an adequate dose to the lung in a convenient number of inhalations. ...<u>Clearly, there is a need for efficient systems that can deliver 5 mg or more of active drug in a single bolus inhalation</u>.

Cipolla, D., *et al.*, Respiratory Drug Delivery VII:231-239 (2000), page 232, lines 4-32, citations omitted; Reference AS, of record).

In contrast to the characterization of the "AIR" technology by Cipolla *et al.*, Applicant teaches a method of delivering particles comprising an agent to the pulmonary system, in a single breath-activated step, wherein the particles deliver at least 5 milligrams of the agent. In addition, Applicant's specification teaches that the particles of the invention can comprise a significant % of bioactive agent (e.g., 58/38.5/3.5: human growth hormone (hGH)/DPPC/Sodium Phosphate (Specification, page 29, lines 25 to page 30, line 3) while still retaining the properties that make them highly dispersible and capable of highly efficient delivery to the pulmonary system.

For example, Example 1 of Applicant's specification teaches that the particles of the invention possess properties which make them highly dispersible and therefore able to achieve high-efficiency delivery from a simple breath-activated device. Specification, page 29, line 8 to page 33, line 6. As described above, Example 1 further teaches a particle composition comprising human growth hormone (hGH) in a 58/38.5/3.5: hGH/DPPC/Sodium Phosphate ratio, which represents a significant % of bioactive agent. Specification, page 29, line 25 to page 30, line 3. In Example 2, Applicant teaches that the highly dispersible particles of the invention can efficiently emit and penetrate into the lungs from a variety of breath-activated Dry Powder Inhalers (with each of the inhalers tested, approximately 50% or more of the emitted dose displayed a mean aerodynamic diameter less than 4 μm in size, thereby indicating that the powder would efficiently enter the lungs of a human subject at a physiological breath rate). Specification, page 33, line 7 to page 34, line 7. In Example 3, Applicant performed *in vivo* scintigraphy to demonstrate that the average lung deposition of the particles of the invention was 59% (relative to the nominal dose). Specification, page 34, line 8 to page 37, line 21. In Example 4, Applicant teaches that the highly dispersible particles of the invention can be used to deliver a surprisingly high dose of drug to the lungs with the same efficiency as a small drug dose (the fine particle fraction <6.8 μm relative to the total dose (FPF_{TD}<6.8 μm) for a small pre-metered dose (6 mg) was 74.4% and for a large pre-metered dose (50 mg) was 75.0%). Specification, page 37, line 22 to page 38, line 9. Thus, it is clear from these Examples that the particles disclosed in Applicant's specification are capable of being used in a method of delivering a therapeutic dose of a bioactive agent to a subject's respiratory tract in a single breath wherein at least about 5 milligrams of the bioactive agent is delivered to the pulmonary system of the subject.

In contrast, Maa *et al.* do not teach or suggest a method of pulmonary delivery that meets the limitations of Applicant's claims. Instead, as described above, Maa *et al.* teach and exemplify that the measured physical, aerodynamic and flow properties of their powder preparations (e.g., agglomeration, flowability, fine particle fraction) are due to the presence of large lactose carrier particles (which are present in a 10:1 weight ratio of lactose carrier:powder) in their blended preparations. Given the teachings of Maa *et al.*, the person of ordinary skill in the art would not have had a reasonable expectation of success utilizing the blended preparations

taught by Maa *et al.* to deliver in a single breath at least about 5 milligrams of the bioactive agent to the pulmonary system of the subject. This is because the very high percentage of lactose carrier present in the blended preparations taught by Maa *et al.* would necessitate exceedingly large pre-metered doses in order to attempt to obtain delivery of at least about 5 milligrams of the bioactive agent to the pulmonary system of the subject in a single breath. In addition, Maa *et al.* further teach that excipient-free protein powders suffered significant aggregation upon spray freeze drying (21.6% for rhMAb and 13.6% for rhDNase) but that aggregation could be decreased by including excipients in the formulations (Maa *et al.*, column 21, line 44 *et seq*). The addition of excipients in the formulation would lower the amount of drug and would require that a greater percentage of the drug-containing particles (present in a 10:1 weight ratio of lactose carrier:drug-containing particles in the blended preparations taught by Maa *et al.*) reach the pulmonary system in order to attempt to obtain delivery of at least about 5 milligrams of the bioactive agent in a single breath. Given these teachings of blended preparations containing mostly large lactose carrier particles and the problems associated with aggregation of particles (see, e.g., Maa *et al.*, column 21, line 44 *et seq*. and column 27, lines 6-25), it is clear that a person of ordinary skill in the art would not have had a reasonable expectation of success utilizing the blended preparations taught by Maa *et al.* to deliver in a single breath at least about 5 milligrams of the bioactive agent to the pulmonary system of the subject. Accordingly, no *prima facie* case of obviousness has been established.

In view of the foregoing, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-3, 8, 9, 18 and 19 Under The Judicially Created Doctrine of Obviousness-Type Double Patenting

The Examiner has rejected Claims 1-3, 8, 9, 18 and 19 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of U.S. Patent No. 6,136,295 ("the '295 Patent"). The Examiner states that although the conflicting claims are not identical, they are not patentably distinct from each other because the '295 Patent claims that at least 50% of the particles have a tap density of less than 0.1 g/cm^3, which is a required

property for flowable delivery of particles to the respiratory tract. Office Action, page 5, lines 6-9.

Independent Claim 1 has been amended to recite "a) at least 50% of the particles have a fine particle fraction less than 4.0 μm; and/or b) at least 75% of the particles have a fine particle fraction less than 6.8 μm," thereby obviating the double patenting rejection. As amended, Applicant's claimed method of delivering a therapeutic dose of a bioactive agent to the pulmonary system of a subject, in a single, breath-activated step is patentably distinct from the method claimed in the '295 Patent (e.g., the limitation specifying the fine particle fraction that is claimed in the method of the instant invention is not claimed in the '295 Patent).

Provisional Rejection of Claims 1-44 Under The Judicially Created Doctrine of Obviousness-Type Double Patenting

The Examiner has also provisionally rejected Claims 1-44 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending U.S. Application No. 09/878,146 (Attorney Docket No. 2685.2001-003). The Examiner states that although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter in both sets of claims is the same. Office Action, page 5, lines 11-15.

As stated by the Examiner, this is a provisional obviousness-type double patenting rejection because the claims deemed to be conflicting have not yet been patented. Thus, if this provisional rejection is the only rejection remaining after entry and consideration of this Amendment, Applicants respectfully request that the Examiner withdraw the rejection and permit the subject application to issue as a patent, in accordance with U.S. Patent Office procedure (see, MPEP § 804(I)(B), p. 800-19, Edition 8 (August, 2001)). Applicants will consider filing a terminal disclaimer and/or otherwise address this rejection of the claims in U.S. Application No. 09/878,146 (Attorney Docket No. 2685.2001-003) at that time.

Information Disclosure Statements

Applicants thank the Examiner for including initialed copies of the Information Disclosure Statements provided by Applicants. However, it is noted that the Examiner has not

initialed references AI (U.S. 5,997,848), AJ (U.S. 6,136,295) and AK (U.S. 5,985,309) on the Information Disclosure Statement filed on January 25, 2001. The Examiner has also not provided an initialed copy of the Second Supplemental Information Disclosure Statement which cited non-published pending U.S. Application Nos. 09/665,252, 09/877,734, 09/382,959 and 09/835,302 (see page 3 of Second Supplemental Information Disclosure Statement filed on February 22, 2002). In addition, a Fourth Supplemental Information Disclosure Statement was mailed on October 22, 2002 citing references AI2-AK2, AA3 and AQ2, and non-published pending application 09/878,146 (see page 3 of Fourth Supplemental Information Disclosure Statement mailed on October 22, 2002). The Examiner is respectfully requested to provide initialed copies of these documents indicating that the Examiner has considered these references and pending applications.

A Fifth Supplemental Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the IDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

New Claims 45-51 have been added.

1. (Twice Amended) A method of delivering a therapeutic dose of a bioactive agent to the pulmonary system of a subject, in a single, breath-activated step, comprising:

administering particles comprising a bioactive agent, from a receptacle having a mass of particles, to a subject's respiratory tract,

wherein:

i) the particles administered to the subject's respiratory tract have a tap density of less than 0.4 g/cm^3;

ii) a) at least 50% of the particles have a fine particle fraction less than 4.0 μm; and/or

b) at least 75% of the particles have a fine particle fraction less than 6.8 μm; and

iii) [deliver] at least about 50% of the mass of particles stored in the receptacle is delivered to the pulmonary system of the subject.

20. (Twice Amended) A method of delivering a therapeutic dose of a bioactive agent to the pulmonary system of a subject, in a single breath, comprising:

administering dry powder particles comprising a bioactive agent, from a receptacle having a mass of particles, to a subject's respiratory tract in a single breath,

wherein:

i) the particles have a tap density less than about 0.4 g/cm^3; and

ii) [deliver] at least about [10] 5 milligrams of the bioactive agent is delivered to the pulmonary system of the subject.